

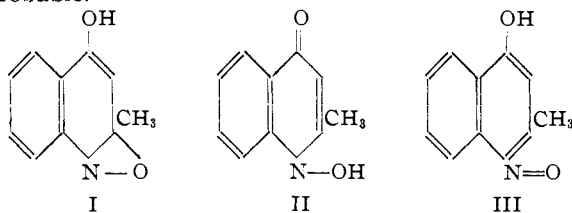
[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO]

SOME NEW DERIVATIVES OF QUINALDINE^{1,2}

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A few months ago, Gabriel and Gerhard³ described a somewhat unusual product, 4-hydroxy quinaldine oxide, obtained in the reduction of *o*-nitrobenzoyl-acetone. They offer rather good evidence that the second oxygen is in combination with nitrogen, and suggest three tentative formulas for the substance, the first and third being considered by them as the most probable.



At the time the articles cited were received, the writer had nearly completed an investigation of a peculiar product obtained in the reduction, by tin chloride and hydrogen chloride in acetic acid, of ethyl *o*-nitrobenzoyl-aceto-acetate, and had under investigation the product described by the above authors. The results, which are here given, in part confirm those of Gabriel and Gerhard, but also extend them considerably, and suggest certain modifications of the structures they have proposed.

Ethyl *o*-nitrobenzoyl-aceto-acetate⁴ was reduced with stannous chloride and dry hydrogen chloride in acetic acid. Formic acid worked less well, and zinc, tin or magnesium in the latter acid were quite ineffective. As products of reduction and condensation, those obviously possible were 4-hydroxyquinaldine, ethyl 4-hydroxyquinaldine-carboxylate, 3,4-dihydroxyquinaldine and the 3-acetyl derivative of the last. None of these was obtained, but instead a product, in almost quantitative yield, which contained one atom of oxygen per molecule in excess of that required for the second-named substance. This, retaining Gabriel and Gerhard's nomenclature, is referred to as 3-carbethoxy-4-hydroxyquinaldine oxide, and is the substance they were unable to obtain by reducing the ester in question with phosphorus and hydriodic acid.

When hydrolyzed, this compound readily gave the corresponding acid, and the latter, on dry-heating, lost carbon dioxide and yielded

¹ This paper is a part of the dissertation presented by K. Lucille McCluskey in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

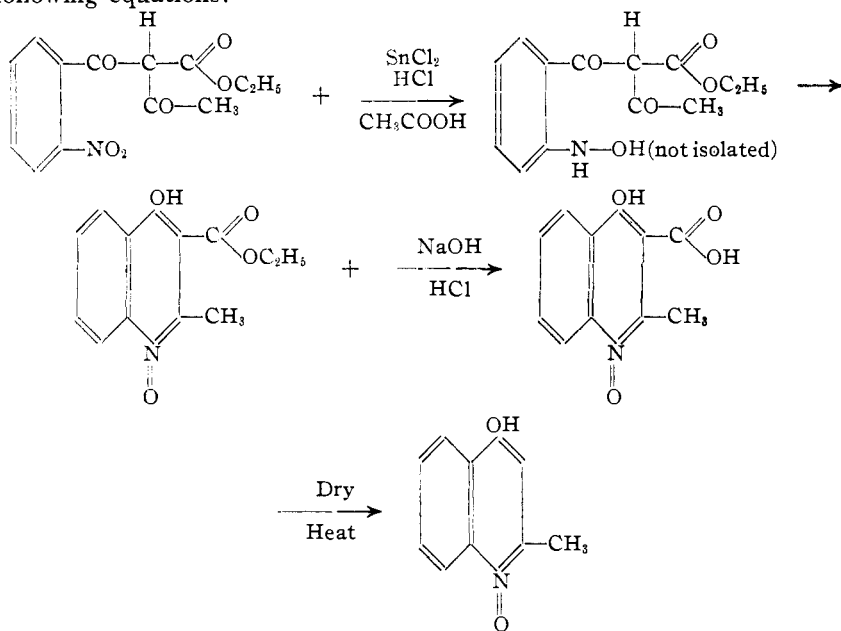
² Acknowledgment is here made to Ben H. Nicolet for appreciated suggestions and encouragement in the course of this work.

³ Gabriel and Gerhard, *Ber.*, **54**, 1067, 1615 (1921).

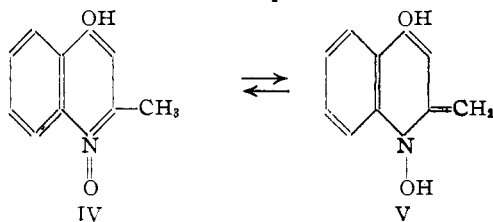
⁴ Needham and Perkin, *J. Chem. Soc.*, **85**, 154 (1904).

4-hydroxyquinaldine oxide, which was shown to be identical with the product of Gabriel and Gerhard by the preparation of its picrate, chloroplatinate and monobenzoate.

The reaction is assumed to take place in the manner indicated by the following equations:



The fact that 4-hydroxyquinaldine oxide is reduced by zinc and hydrochloric acid to 4-hydroxyquinaldine, adds to the evidence already available, that one of the oxygens must be attached to nitrogen. The observation, however, that a dibenzoate of 4-hydroxyquinaldine (which was isolated and analyzed) can be prepared, requires some modification in the formulas for this oxide given by Gabriel and Gerhard; that is, it becomes necessary to consider a formula which indicates the presence of two hydroxyl groups in the molecule. This may be considered as in equilibrium with at least one of the forms suggested above (probably III); the difference between the two hydroxyl groups is clearly brought out by the fact that one of the benzoyl groups is removed by hydrolysis on crystallization from 50% acetic acid. The structure preferred for the oxide is accordingly



Experimental Part

***o*-Nitrobenzoyl Chloride.**—It was found that *o*-nitrobenzoyl chloride could be best prepared from thionyl chloride and *o*-nitrobenzoic acid according to the method of Auvers and Duesberg.⁵ To 100 g. of pure thionyl chloride, protected from moisture, 50 g. of *o*-nitrobenzoic acid was added in small portions, and the mixture warmed after each addition to 80° to start reaction. The reaction mass was allowed to stand at room temperature for 8 hours, then heated for 15 minutes on a water-bath under a reflux condenser. The unused thionyl chloride, hydrogen chloride and sulfur dioxide were then removed by distillation from a water-bath under reduced pressure.

Ethyl *o*-Nitrobenzoyl-aceto-acetate.—The best yield of ethyl *o*-nitrobenzoyl-aceto-acetate as well as the purest product was obtained in the following manner: *o*-nitrobenzoic acid, prepared from thionyl chloride and *o*-nitrobenzoic acid, was condensed with freshly distilled aceto-acetic ester by means of sodium ethylate according to the Needham and Perkin⁶ method, but the products of the reaction were allowed to stand well protected from moisture for only 4 to 5 hours in an ice-bath instead of "overnight at the ordinary temperature" as directed by the above mentioned authors.

The separated yellow crystalline sodium salt of ethyl *o*-nitrobenzoyl-aceto-acetate was collected and treated as suggested by Needham and Perkin. The ethyl *o*-nitrobenzoyl-aceto-acetate was obtained in good yield as a very light reddish-brown oil.

Ethyl 4-Hydroxy-3-quinaldine-carboxylate Oxide.—Seventy-one g. of hydrated stannous chloride was added to 225 cc. of glacial acetic acid and dry hydrogen chloride was introduced until the solution became clear. To this solution was added 14.8 g. of ethyl *o*-nitrobenzoyl-aceto-acetate, and the introduction of hydrogen chloride continued. The contents of the flask were stirred with a turbine throughout the entire operation. In time a white crystalline substance separated and the reduction was continued until the reaction mass had cooled to room temperature. The precipitate was collected, washed first with water containing a little acetic acid, and then with water. In the above experiment 13.8 g. of the crude product was obtained. The ester was purified by dissolving in warm 95% alcohol and precipitating with water. For analysis this substance was dried *in vacuo* over sulfuric acid.

Analyses. Subs., 0.1888: CO₂, 0.4389; H₂O, 0.0936. Subs., 0.4230: 21.00 cc. of dry N₂ (22° and 733.2 mm.). Calc. for C₁₃H₁₃NO₄: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.43; H, 5.51; N, 5.56.

The chloroplatinate, melting with decomposition at 203°, gave the following analysis.

Analysis. Subs., 0.1250: Pt, 0.0279. Calc. for (C₁₃H₁₄NO₄)₂PtCl₆: Pt, 22.49. Found: 22.32.

Ethyl 4-hydroxy-3-quinaldine carboxylate oxide is a white crystalline substance melting without decomposition at 174°. It is easily soluble in alcohol, chloroform, acetone, sodium hydroxide, ammonium hydroxide, sodium carbonate and strong hydrochloric acid, slightly soluble in benzene, cold dil. hydrochloric acid and bicarbonate and almost insoluble in water, ether, and ligroin. An alcoholic solution gives with ferric chloride a reddish-brown coloration. It reduces ammoniacal silver nitrate but not Fehling's solution, and decolorizes an acetone solution of potassium permanganate.

4-Hydroxy-3-quinaldine-carboxylic acid Oxide.—The acid was prepared from the ester by hydrolysis with alkali. To 3 g. of pure ethyl 4-hydroxy-3-quinaldine-carboxylate oxide was added 2.4 g. of sodium hydroxide dissolved in 100 cc. of water; the resulting solution was heated under a reflux condenser for 2 hours. It was then allowed to

⁵ Auvers and Duesberg, *Ber.*, **53**, 1207 (1920).

⁶ Needham and Perkin, *J. Chem. Soc.*, **85**, 154 (1904).

cool, diluted with twice its volume of water, filtered and the acid precipitated with hydrochloric acid. From the above experiment 2.5 g. of the crude acid was obtained. It was purified by crystallizing from hot absolute alcohol in which it is difficultly soluble. For analysis the compound was recrystallized from absolute alcohol and dried *in vacuo* over sulfuric acid to constant weight.

Analyses. Subs., 0.2007: CO₂, 0.0440; H₂O, 0.0819. Subs., 0.3489: 20.10 cc. of dry N₂ (26° and 730.4 mm.). Calc. for C₁₁H₉NO₄: C, 60.26; H, 4.14; N, 6.39. Found: C, 59.90; H, 4.54; N, 6.33.

4-Hydroxy-3-quinaldine-carboxylic acid oxide is a dull white substance decomposing at 209° with loss of carbon dioxide to give 4-hydroxy-quinaldine oxide. It is easily soluble in sodium hydroxide, sodium carbonate and ammonium hydroxide, rather difficultly soluble in alcohol, acetone and bicarbonate, and insoluble in chloroform, benzene, ligroin, and ether. It reduces ammoniacal silver nitrate but does not reduce Fehling's solution. An alkaline solution quickly decolorizes potassium permanganate giving an emerald-green solution.

4-Hydroxyquinaldine Oxide.—For the preparation of the 4-hydroxyquinaldine oxide from 4-hydroxy-3-quinaldine-carboxylic acid oxide it was found advantageous to work with quantities not larger than 1 to 1.5 g. The acid contained in a hard glass test-tube was immersed in a glycerine bath previously heated to 209°, until the evolution of carbon dioxide had practically ceased. The residue was dissolved in a 1% solution of sodium hydroxide. After filtering, the solution was decolorized with charcoal and the 4-hydroxyquinaldine oxide precipitated with carbon dioxide. From 10 g. of acid 6.5 g. of the crude 4-hydroxyquinaldine oxide was obtained. This substance was recrystallized twice from hot methyl alcohol, dried to constant weight over sulfuric acid and analyzed for nitrogen.

Analysis. Subs., 0.2899: 20.6 cc. of dry N₂ (23° and 738.3 mm.). Calc. for C₁₀H₉NO₂: N, 7.99. Found: 7.97.

The 4-hydroxyquinaldine oxide does not give a sharp melting point. It softens at 245° and gives a dark melt at 247° with foaming. It is easily soluble in glacial acetic acid, dil. acids, and alkalis, quite difficultly soluble in alcohol, very slightly soluble in water, and insoluble in ether, acetone, chloroform, benzene, ligroin, anisol, ethyl acetate, and diphenyl ether. An alcoholic solution is colored by ferric chloride. It reduces ammoniacal silver nitrate very easily but does not reduce Fehling's solution. A very dilute sulfuric acid solution of the quinaldine oxide immediately decolorizes potassium permanganate, giving a yellow solution.

Derivatives of 4-Hydroxyquinaldine Oxide.—The yellow crystalline chloroplatinate melts definitely between 229° and 230°, although it darkens somewhat at about 200°. It was analyzed for platinum.

Analysis. Subs., 0.2155: Pt, 0.0548. Calc. for (C₁₀H₁₀NO₂)₂PtCl₆: Pt, 25.67. Found: 25.44.

The **picrate** was prepared by bringing together an alcoholic solution of equivalent amounts of the 4-hydroxyquinaldine oxide and picric acid. After crystallizing from hot water, the picrate melted at 171° which agrees with the picrate of Gabriel and Gerhard's "oxy base."

DIBENZOYL DERIVATIVE.—The dibenzoyl derivative was obtained by shaking an alkaline solution of 4-hydroxyquinaldine oxide with the calculated amount of benzoyl chloride suspended in benzene. After the reaction mass was allowed to stand for some time with frequent shaking, an oily by-product which was formed in small amount was removed with ether, and the benzoylated compound collected upon a filter. For analysis, it was crystallized from hot 95% alcohol, dried *in vacuo* over sulfuric acid to constant weight and analyzed for nitrogen.

Analysis. Subs., 0.3587: 12.3 cc. of dry N₂ (24° and 735.8 mm.). Calc. for C₂₄H₁₇NO₄: N, 3.66. Found: 3.80.

The dibenzoyl derivative is a white crystalline substance melting sharply at 171° to give a clear liquid. It is soluble in warm alcohol, and easily soluble in acetone from which it can be precipitated by water; it is insoluble in alkalis. An acetone solution does not decolorize potassium permanganate nor reduce silver nitrate.

MONOBENZOYL DERIVATIVE.—When the dibenzoyl compound is crystallized from 50% acetic acid a white solid is obtained which melts at 236°. This corresponds to Gabriel and Gerhard's⁷ monobenzoyl derivative of their "oxy base."

Reduction of 4-Hydroxyquinaldine Oxide to 4-Hydroxyquinaldine.—The hydroxyquinaldine oxide was dissolved in dil. hydrochloric acid and a small amount of conc hydrochloric acid was added. Zinc dust was then added in small quantities at short intervals with gentle warming to start the reaction. When the reduction was complete, sodium carbonate was added in excess, and the whole heated to boiling and filtered hot from the unused zinc and zinc carbonate. The filtrate was evaporated to a small volume and made slightly acid with acetic acid. A white solid separated which was crystallized from boiling water and dried at 110°.

This substance was identified as 4-hydroxyquinaldine by comparison with 4-hydroxyquinaldine prepared from ethyl β-phenyl-aminocrotonate according to Conrod and Limpach.⁸ A melting point of a mixture of 4-hydroxyquinaldine prepared by these two methods showed no depression. Further identification was made through the picrates.

Reduction of *o*-Nitrobenzoyl-acetone.—The *o*-nitrobenzoyl-acetone was prepared from ethyl *o*-nitrobenzoyl acetate according to Gevekoht.⁹

For 2 g. of *o*-nitrobenzoyl-acetone, melting at 55°, 9 g. of hydrated stannous chloride and 30 cc. of glacial acetic acid were used. The procedure was exactly the same as in the reduction of the ethyl *o*-nitrobenzoyl-aceto-acetate given above. In a short time a brilliant yellow crystalline solid had separated. This very likely is the tin chloride double salt. This substance was collected, dissolved in water, acidified slightly with hydrochloric acid and the tin removed with hydrogen sulfide. The filtrate was evaporated to small volume and neutralized carefully. The precipitated solid was crystallized from hot alcohol. It softened slightly at 245° and melted completely at 247° giving a dark melt. A melting point of a mixture of this compound with that of 4-hydroxyquinaldine oxide, prepared from 4-hydroxy-3-quinaldine carboxylic acid oxide showed no depression. Further identification was made through the picrate.

Thus the *o*-nitrobenzoyl-acetone so reduced yields 4-hydroxyquinaldine oxide.

Summary

1. The 4-hydroxyquinaldine oxide of Gabriel and Gerhard has been independently obtained by a rather different method.
2. Certain related derivatives which the above mentioned authors were not able to obtain, are also described.
3. The formation of a dibenzoyl derivative of the above substance, permits and requires a partial modification of the structure previously assigned to it.

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⁷ Ref. 3, p. 1067.

⁸ Conrod and Limpach, *Ber.*, **20**, 947 (1887).

⁹ Gevekoht, *Ann.*, **221**, 323 (1883).